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1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/521,313	LEE ET AL.	
	Examiner	Art Unit	
	Kevin K. Hill, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 July 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28* is/are pending in the application.

4a) Of the above claim(s) *4-10* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 11-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

Amendments

In the reply filed July 17, 2007, Applicant has withdrawn Claims 4-10, amended Claims 1, 3, 13 and16, and added new claims, Claims 19-28.

Claims 4-10 are pending but withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a non-elected invention, there being no allowable generic or linking claim.

Claims 1-3 and 11-28 are under consideration.

Priority

This application is a 371 of PCT/KR03/01400, filed July 15, 2003, and claims priority to KR 10-2002-0041764, filed July 15, 2002 and KR 10-2003-0038012, filed June 12, 2003.

Acknowledgment is made of Applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d).

Response to Amendment

In the response filed July 17, 2007, Applicant has submitted a certified translation of Korean Patent Application No. 10-2002-0041764, filed July 16, 2002 and Korean Patent Application No. 10-2003-0038012, filed June 12, 2003.

Accordingly, the effective priority date of the instant application is granted as July 16, 2002.

Examiner's Note

Unless otherwise indicated, previous objections/rejections that have been rendered moot in view of the amendment will not be reiterated. The arguments in the July 17, 2007 response will be addressed to the extent that they apply to current rejection(s).

Claim Objections

1. **Claim 16 is objected to because of the following informalities**: The claim is missing the preposition "to" after "the step of administering".

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. **Claim 16 stands and Claims 19-28 are rejected under 35 U.S.C. 112, first paragraph**, because the specification, while being enabling for methods of preventing or treating cancer, inducing antitumor immunity, reducing tumor growth, decreasing tumor metastasis and prolonging survival period in a rodent, the method(s) comprising the step of administering by intramuscular injection an effective amount of a DNA vaccine composition comprising a pTV2 vector or pCK vector which comprises a nucleotide sequence encoding a truncated human Her-2/neu protein, said truncated human Her-2/neu protein lacking an intracellular domain, and wherein said DNA vaccine composition further comprises nucleic acid encoding the cytokine granulocyte-macrophage colony-stimulating factor (GM-CSF), does not reasonably provide enablement for a method of preventing or treating an enormous genus of etiologically and pathologically distinct cancers in an enormous genus of mammalian subjects, including humans. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

This rejection is maintained for reasons of record in the office action mailed April 6, 2007 and re-stated below. The rejection has been re-worded slightly based upon Applicant's amendment filed July 17, 2007.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention. If not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (*In re Wands*, 858 F.2d 731, 737, 8 USPQ2ds 1400, 1404 (Fed. Cir. 1988)). Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification. Therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention. And thus, skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

The Breadth of the Claims and The Nature of the Invention

With respect to the method, the claim is broad for encompassing treatment methods as applied to an enormous genus of subjects, including mammals, specifically humans, wherein Applicant contemplates an enormous genus of DNA vaccine formulations and administration means, for example, aerosol formulation/administration, parenteral injection, suppositories, and oral formulations (pgs 9-10). It is noted that claims 19-28 do not limit the subject to mammalian organisms, and thus reasonably encompass vertebrate and invertebrate organisms that may be hosts to human tumor cells (xenotransplantation) in experimental research model systems.

With respect to the DNA vaccine composition, the breadth of the claim is exceptionally large for encompassing a genus of structurally distinct nucleic acid compositions encoding structurally and biologically distinct polypeptides for use as a DNA vaccine for the treatment and/or prevention of an enormous genus of etiologically and pathologically distinct cancers, including carcinoma of the breast, prostate, ovary, uterus, stomach and adenocarcinoma of the lung.

When the claims are analyzed in light of the specification, the inventive concept of the instant application is to provide a DNA vaccine composition for preventing or treating cancer, wherein the specification discloses that Her-2/neu is amplified and over-expressed in several types of human adenocarcinomas, especially tumors of the breast and ovary. Thus, the Her-2/neu oncogene is an excellent target for the development of therapeutic vaccines specific for Her-2/neu-over-expressing human cancers (pg 1, lines 15-28).

The State of the Prior Art, The Level of One of Ordinary Skill and The Level of Predictability in the Art

Her-2/*neu* is an oncogene coding for a transmembrane protein (p185neu) and belonging to the family of tyrosine kinase growth factor receptors. Her-2/*neu* gene amplification and consequent over expression of Her-2/*neu* receptor have been observed in a significant proportion of human cancers including carcinoma of the breast, prostate, ovary, uterus, stomach and adenocarcinoma of the lung and is intimately associated with malignant phenotype and aggressiveness of the malignancy. The relevant art of the instant invention is DNA vaccines, wherein the level of skill for an ordinary artisan is high.

DNA Vaccine

At the time of the instant application (priority date of July, 2002), limited data was available regarding DNA vaccination in humans. In the early trials, eliciting anti-tumor immunity in cancer patients using DNA vaccines has proved more difficult, and little evidence of anti-tumor immunity was demonstrated using first generation tumor antigen DNA vaccines.

DNA vaccine model represents a promising, practical and effective way to elicit immune responses against an antigen expressed by malignant cells. An issue in developing tumor DNA vaccines is to design protocols that can be translated from murine models to large animal models and clinical human use without losing their potency (Smorlesi et al, Vaccine 24: 1766-1775, 2006, pg 1767, col. 1, ¶1). The quality of the immune response elicited by a DNA vaccine is also dependent by the procedure of DNA delivery that influences the mechanisms of DNA uptake, transgene expression, and transgene product processing. The results of tumor antigen DNA vaccine approaches might be improved by optimization of key variables such as dosage, route,

vector design, and boosting strategies. Thus, the role of the DNA delivery system on the outcome of the vaccine should be considered in the elaboration of a HER2/*neu* DNA vaccine.

The efficacy of DNA vaccine against HER2/*neu* is influenced by the method of release of DNA. Smorlesi et al showed that vaccine delivery methods, e.g. intramuscular injection, electroporation, and gene gun, elicited diverse immune mechanisms that differently prevented the appearance and the development of spontaneous mammary carcinomas (Smorlesi et al; pg 1773, col. 1, ¶1). The art also recognizes that the non-obvious use of a particular promoter for required expression in the desired cell type. For example, SV40, although a relatively strong promoter in fibroblasts and epithelial cell types, may be weaker than the commonly used cytomegalovirus promoter. (Chen et al, Clinical Cancer Research 6: 4381-4388, 2000; pg 4385, col. 2).

Many of the experimental systems used to evaluate the efficacy of DNA vaccine against tumor progression suffer several drawbacks, for example, immunization of healthy animals against a subsequent challenge with tumor cells was assayed rather than treatment of a tumor-bearing animal with DNA vaccine. However, patients with established, rapidly growing tumors can have an impaired cellular and humoral immune system. Therefore, it might be difficult to activate immunological defense mechanisms by vaccination (Bernhard et al, Society for Endocrinology 9(1): 33-44, 2002; pg 40, col. 1, ¶1). Moreover, while the amount of produced antibodies only partially correlate with the outcome of vaccination, the quality of humoral response seems to be determinant for the success of vaccination. Immunized mice can develop anti-Her-2/neu antibody, as demonstrated by Western blotting, but are provided no protection from tumor progression (Chen et al; pg 4385, col. 2, lines 15-17). Therefore, it is likely that DNA vaccine against a specific tumor-associated antigen may not be sufficient by itself to prevent progression of native pre-existing tumor.

The art also recognizes that a number of concerns exist with respect to immunizing with Her-2/neu vaccines. For example, once concern is that the polyclonal humoral response generated may contain immunoglobulins that can activate the Her-2/neu receptor, as has been found with some monoclonal antibodies, and lead to increased cell growth rather than inhibition (Esserman et al, Cancer Immunol. Immunther. 47: 337-342, 1999; pg 340, col. 2, ¶3). Furthermore, it is possible that increasing the anti-Her-2/neu immunity to a level necessary to destroy cancer tissue *in vivo* may also increase levels of autoimmune reactivity against normal tissues to the point of inducing toxicity (pg 341, col. 1, lines 17-21).

Animal models

Most DNA vaccine investigations are performed in models of implanted tumors that consist of the challenge of mice with a bolus of tumor cells giving rise to a fast and unnaturally growing tumor. Furthermore, the roles of p185Her-2/neu on tumor growth and immunomodulation may be altered in tumors over-expressing rat or human p185Her-2/neu. The therapeutic response may thus depend on the type of vaccine administered as well as the cancer cells used in the animal study (Lin et al, Molecular Therapy 10(2): 290-301, 2004; pg 296, col. 1, lines 11-14). Therefore, the efficacy of Her-2/neu DNA vaccine must be tested on mouse tumor cells natively over-expressing mouse p185Her-2/neu (Lin et al, pg 291, col. 1, ¶1). The art recognizes that transgenic mice reproduce the more complex spontaneous progression of a pre-neoplastic lesion and their use provides information that may be more relevant to cancer

development in humans where the tumor is initiated by the clonal expansion from a single cell *in vivo* (Smorlesi et al; pg 1767, col.s 1-2, joining ¶). For example, the *Her-2/neu* transgenic mice possess distinct kinetics of disease development that better reflect spontaneous mammary carcinogenesis and recapitulate a few features of the development of human mammary carcinoma.

Although the results using plasmid DNA vaccines against HER2 have been promising in rodent models, there are drawbacks when considering the use of plasmid DNA vaccines in humans. The major drawback to the use of plasmid DNA vaccines in humans is that, although proven to be quite effective in rodents, DNA-based vaccines have generally performed poorly in both non-human primate studies as well as in human clinical trials. Thus, until formulation and delivery technologies are developed to increase the potency of plasmid DNA vaccines in humans, this approach is not likely to be an optimal one for human vaccines (Foy et al, Seminars in Oncology 29(3 Suppl. 11): 53-61, 2002; pg 56, col. 2, ¶1). Furthermore, the art recognizes that FVB and BALB/c mice used for testing experimental DNA vaccines may not be representative for the human scenario (Chang et al, Int. J. Cancer 111: 86-95, 2004; pg 86, col. 1, last sentence). In the case of human Her-2/neu in human patients, the artisan may not reasonably extrapolate the ability to breakdown tolerance and induce an effective immune response, as achieved in animal models, because Her-2/neu is a self-tolerated antigen widely expressed at low levels in multiple tissues in humans.

Cytokine therapy

Cytokine genes have been used in many studies to enhance the immune response to a DNA vaccine against a specific antigen. Fusion genes or co-delivery of cytokine genes can augment the immune response and influence the immune pathway. The anti-tumor responses induced by different cytokines seemed to operate through different mechanisms. For example, cytotoxic CD8+ T cells play a major role in the IL-2-induced immune response (15), whereas CD4+ and CD8+ T cells mediate the GM-CSF anti-tumor activity (Chen et al; pg 4381, col. 2, ¶1). Although several studies have indicated that GM-CSF had a strong capacity to enhance the effects of DNA vaccines by amplifying both cellular and humoral immunity, the benefit of co-administration of cytokine genes is dependent on the nature of tumor-associated antigen and the intrinsic immunologic properties of tumor cells (Lin et al; pg 298, col. 1, ¶1).

Thus, the art recognizes significant unpredictability regarding the design of any Her-2/neu DNA vaccine, with or without combined administration of nucleic acids encoding a cytokine, to reliably prevent or treat an enormous genus of etiologically and pathologically distinct tumors in an enormous genus of mammalian organisms, including mice and humans. The art speaks to the lack of standards in animal models, the difficulties to adequately mimic the complex disease pathologies observed in humans to the animal model system, and the general inability to reliably extrapolate results achieved in the rodent system to the primate system.

The Existence of Working Examples and The Amount of Direction Provided by the Inventor

The specification teaches the tumor challenge in laboratory BALB/c mice by injection of suspended human breast carcinoma cells or murine colon adenocarcinoma cells (pg 13, lines 1-5), wherein said cells either administered subcutaneously on the flank or intravenously (pg 15,

lines 29-30). Applicant contemplates an enormous genus of DNA vaccine formulations and administration means (pgs 9-10); however, only intramuscular injection is disclosed as an effective administration means of vaccination. The specification also does not teach the structural nature of the expression plasmids; merely disclosing that the pCK vector has a stronger promoter activity than pTV2 (pg 22, line 18). Furthermore, the claims reasonably embrace a pTV2Neu$_{TM}$-GMCSF bi-cistronic expression plasmid (Claims 11 and 17), yet no such plasmid is disclosed in the specification. The inventive DNA vaccines are administered either before or after the tumor challenge by intramuscular injection. Under experimentally controlled conditions, the vaccinated mice were able to generate antibodies to the Her-2/neu antigen (Example 3), suppress tumor challenge, exhibit decreased frequency of tumor metastasis, and prolonged survival periods (Examples 4-6).

The specification fails to disclose that the inventive method is capable of achieving the clinically desirable results as per spontaneous tumor formation, which is the clinically relevant condition, in any other mammal, including primates such as humans. Such guidance is important in light of the wealth of data in the art teaching the inability to predictably extrapolate the instant rodent model to humans.

The Quantity of Any Necessary Experimentation to Make or Use the Invention

Thus, the quantity of necessary experimentation to make or use the invention as claimed, based upon what is known in the art and what has been disclosed in the specification, will create an undue burden for a person of ordinary skill in the art to demonstrate that the instantly claimed DNA vaccine compositions can prevent or treat an enormous genus of etiologically and pathologically distinct cancers, as contemplated by Applicant and reasonably embraced by the claims, via the enormous genus of contemplated composition formulations and administration means because the critical and essential elements of the DNA vaccine expression plasmids are not disclosed so as to guide an artisan how to make the DNA vaccine compositions and effectively target the nucleic acid to the desired cell types so as to effect the immunological response. Furthermore, the art recognizes that the model system disclosed, wherein a bolus of tumor cells is administered to the host, does not adequately represent the clinical condition wherein a patient has any one of an enormous genus of genotypically and phenotypically distinct cancers in any one of a multitude of physiologically and pathologically distinct organs and tissues.

In conclusion, the specification fails to provide any guidance as to how an artisan would have dealt with the art-recognized limitations of the claimed method commensurate with the scope of the claimed invention and therefore, limiting the claimed invention to methods of preventing or treating cancer, inducing antitumor immunity, reducing tumor growth, decreasing tumor metastasis and prolonging survival period in a rodent, the method(s) comprising the step of administering by intramuscular injection an effective amount of a DNA vaccine composition comprising a pTV2 vector or pCK vector which comprises a nucleotide sequence encoding a truncated human Her-2/neu protein, said truncated human Her-2/neu protein lacking an intracellular domain, and wherein said DNA vaccine composition further comprises nucleic acid encoding the cytokine granulocyte-macrophage colony-stimulating factor (GM-CSF), is proper.

Applicant's Arguments

Applicant argues that the results obtained in rodents enables the genus of mammals encompassed by the claims because the experiments were performed in a well-established animal model for cancers, and it is predicted that a mammal, including human beings, would produce the same or similar immune responses.

Applicant's argument(s) has been fully considered, but is not persuasive. While applicant argues for the use of an art-recognized animal model, the substantive issue is whether or not the rodent model provides enabling support for a method of preventing or treating an enormous genus of biologically and physiologically distinct mammalian organisms.

As *In re Gardner, Roe and Willey*, 427 F.2d 786,789 (C.C.P.A. 1970), the skilled artisan might eventually find out how to use the invention after "a great deal of work". In the case of *In re Gardner, Roe and Willey*, the invention was a compound which the inventor claimed to have antidepressant activity, but was not enabled because the inventor failed to disclose how to use the invention based on insufficient disclosure of effective drug dosage. The court held that "the law requires that the disclosure in the application shall inform them how to use, not how to find out how to use for themselves".

The art recognizes that gene therapy is an unpredictable art, with potentially deadly unanticipated outcomes (see http://www.washingtonpost.com/wp-dyn/content/article/2007/08/05/AR2007080501636.html?nav%3Dhcmodule&sub=AR for a current example). The art has recognized that many *in vitro* and animal models that are provided as evidence of success of treatment have not translated into successful treatment in humans. Eliciting anti-tumor immunity in [human] cancer patients using DNA vaccines has proved more difficult, and little evidence of anti-tumor immunity was demonstrated. The simple statement advanced by Applicant that the rat model will reasonably predict physiological responses in all other mammals embraced by the claim is inadequate and does not obviate the art-recognized lack of standards in animal models, the unpredictability regarding gene therapy and DNA vaccine technologies to elicit a specific immune response sufficient to achieve a clinically-relevant therapeutic outcome, and the art-recognized limitations of animal models that, although proven

to be quite effective in rodents, DNA-based vaccines have generally performed poorly in both non-human primate studies as well as in human clinical trials.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. **Claim 25 is rejected under 35 U.S.C. 112, second paragraph**, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim is drawn to a method of decreasing tumor metastasis; however, the method step that is to be applied in claim 25 is not recited. Furthermore, the meaning of "after tumor surgery" is unclear because the purpose of the tumor surgery and the type of surgical procedure is neither claimed nor disclosed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

4. **Claims 1-3, 13 and 16 stand and claims 19-28 are rejected under 35 U.S.C. 103(a)** as being obvious over Piechocki et al (J. Immunol. 167: 3367-3374, 2001) and Lee et al (Biochem.

Biophys. Res. Comm. 272(1): 230-235, 2000), as evidenced by Bocchia et al (Haematologica 85: 1172-1206, 2000).

This rejection is maintained for reasons of record in the office action mailed April 6, 2007 and re-stated below. The rejection has been re-worded slightly based upon Applicant's amendment filed July 17, 2007.

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

Piechocki et al teach the use of a plasmid DNA vaccine comprising a nucleotide sequence encoding a truncated human Her-2/neu polypeptide, said polypeptide consisting of an extracellular domain, specifically the amino terminal amino acids 1-505 of the mature human Her-2/neu extracellular domain (pg 3368, col. 1, Construction). Piechocki et al teach a method of preventing or treating cancer, inducing antitumor immunity, as measured by CTL response (pg 3372, Figure 5), reducing tumor growth and prolonging survival period, wherein laboratory BALB/c mice received three intramuscular injections of DNA vaccine prior to challenge with Her-2+ D2F2 murine mammary tumor cells (pg 3369, col. 1, Inhibition of Tumor Growth; pg 3371, Figure 3). Piechocki et al teach that all tumor-free mice at 10 weeks after tumor challenge were capable of rejecting a second tumor challenge, demonstrating sustained immunity to tumor-associated antigens (pg 3370, col. 2, lines 1-8).

Piechocki et al do not teach the tumor cells to be ovarian cancer. However, nothing non-obvious is seen with substituting breast cancer cells with ovary cancer cells because the art recognizes that both breast and ovary cancer cells overexpress Her-2/neu (Piechocki et al, pg

3367, col. 1, ¶1). Thus, the method of inducing antitumor immunity and prolonging survival period of breast cancer via the use of a Her-2/neu DNA vaccine would also be capable of inducing antitumor immunity and prolonging survival period of ovary cancer, absent evidence to the contrary, as the claims recite the breast and ovary cancers as alternatives (an thus essentially equivalent) and there is nothing in the instant disclosure to clearly distinguish method steps designed specifically for treating breast cancer from method steps designed specifically for treating ovary cancer.

Piechocki et al do not explicitly teach a method of decreasing tumor metastasis as per the use of the human Her-2/neu DNA vaccine. However, absent evidence to the contrary, the capability to decrease tumor metastasis is an inherent property of the DNA vaccine and the method steps performed by Piechocki et al that demonstrated prevention and treatment of cancer, induction of antitumor immunity, reduced tumor growth and prolonged survival periods were also sufficient to decrease tumor metastasis because the DNA vaccine is the same and there is no patentable distinction in the method step by which the vaccine is to administered to the subject so as to clearly exclude the clinically effective method of decreasing tumor metastasis from the methods of preventing or treating cancer, inducing antitumor immunity, reducing tumor growth and prolonging survival periods.

To the extent that the purpose of the claimed "tumor surgery" is indefinite (see above), the term "tumor surgery" may be interpreted to reasonably embrace the introduction of tumor cells into the host animal, e.g. tumor challenge in an experimental model, or tumor surgery to remove a primary tumor in a patient. Piechocki et al do not teach the DNA vaccination method to be performed after a method step of tumor surgery, e.g. DNA vaccination after the inoculation and establishment of tumor cells in the experimental animal model. However, at the time of the invention, the art recognized that in the real world clinical setting, human patients will present with tumor disease before being therapeutically treated with a tumor vaccine (Bocchia et al, pg 1174, col. 2, When?, ¶1). Thus, the claim would have been obvious to one of ordinary skill because a person of ordinary skill has good reason to pursue the known options within his or her technical grasp, e.g. common sense. Within the realm of experimental animal models, the artisan would be motivated to administer the DNA vaccine after the tumor surgery that inoculated the tumor cells into the host animal because such a tumor-bearing animal model subsequently treated

with a DNA vaccine (therapeutic vaccination) would more closely reflect the real world clinical reality.

Piechocki et al do not teach the use of a pCK vector. However, at the time of the invention, Lee et al (2000) taught the construction of a pCK expression plasmid that is able to drive high levels of gene expression *in vivo* for therapeutic use. Lee et al teach the use of this vector to express VEGF165 in mice as an example of gene therapy (pg 233, Figure 5).

It would have been obvious to one of ordinary skill in the art to substitute the expression vector of Piechocki et al with the pCK expression vectors as taught by Lee et al with a reasonable chance of success because the Lee et al teach the ability of such vectors for use a gene therapy vehicles. An artisan would be motivated to use the expression vectors of Lee et al because Lee et al teach that, for example, the newly developed pCK vector efficiently expressed the exogenously added gene *in vivo*, and reproducibly produced much higher levels of the target polypeptide than all expression vectors tested so far, including commercially available HCMV IE promoter-based plasmids and those using housekeeping gene promoters. Expression of the heterologous polypeptide lasted at least up to 16 days following a single injection. Furthermore, Lee et al suggest that pCK provides clear advantages over other previously developed plasmids, and would not only significantly increase therapeutic effects at a given dose, but also lower the costs of production, and thus treatment. With respect to the broad applicability for *in vivo* gene therapy, Lee et al anticipate the vector should be useful for gene therapy for any disease that can be treated with a reasonable level of gene expression in a transient manner in a localized area (pg 234, Discussion).

Neither Piechocki et al nor Lee et al teach the use of a pTV2 vector. However, absent evidence to the contrary, nothing non-obvious is seen with replacing one expression vector for another expression vector because the Her-2/neu gene is under the same regulatory control, specifically the CMV promoter, in the pTV2 vector as is also present in the pCK vector, and thus the substitution of a pCK vector for a pTV2 vector would yield predictable results as the vectors are functionally equivalent.

Thus, the invention as a whole is *prima facie* obvious.

Applicant's Arguments

Applicant argues that Piechocki et al and Lee et al do not teach or suggest the elements of the currently presented claims, nor motivate the artisan to employ transmembrane and extracellular domains or extracellular domains of human Her-2/neu protein with a reasonable expectation of success.

Applicant's argument(s) has been fully considered, but is not persuasive.

In response to applicant's argument that the references do not provide that a specific teaching, suggestion, or motivation to support a finding of obviousness, *KSR* forecloses the argument that a specific teaching, suggestion, or motivation is required to support a finding of obviousness. See the recent Board decision *Ex parte Smith*, USPQ2d, slip op. at 20 (Bd. Pat. App. & Interf. June 25, 2007) (citing *KSR International Co. v. Teleflex Inc. (KSR)*, 82 USPQ2sd at 1396) (available at www.uspto.gov/web/offices/dcom/bpai/prec/fd071925.pdf).

Piechocki et al teach the use of a DNA vaccine vector encoding a human Her-2/neu extracellular domain and a method of preventing or treating cancer, a method of inducing antitumor immunity, a method of reducing tumor growth and a method of prolongin survival period, the method(s) comprising the step of administering to a mammal, specifically a mouse, in need of prevention or treatment of cancer with an effective amount of the DNA vaccine encoding a human Her-2/neu extracellular domain. Piechocki et al do not teach a pCK vector; however, Lee et al taught the pCK vector for use in gene therapy. Thus, all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention. Combining the two elements is well within the common sense of the ordinary artisan.

5. **Claims 1, 11-15 and 17-18 stand rejected under 35 U.S.C. 103(a)** as being obvious over Piechocki et al (2001) and Lee et al (2000), as applied to Claims 1, 13 and 16 above, and in further view of Steinna et al (U.S. Patent No. 7,005,498 B1) and Pilon et al (J. Immunol. 167: 3201-3206, 2001; *of record in IDS).

This rejection is maintained for reasons of record in the office action mailed April 6, 2007 and re-stated below. The rejection has been re-worded slightly based upon Applicant's amendment filed July 17, 2007.

The prior cited art does not teach:
i) a DNA vaccine composition comprises a plasmid which expresses a gene encoding a cytokine,
ii) wherein the DNA vaccine vector further comprises a nucleotide sequence encoding a cytokine, or
iii) wherein said cytokine is GM-CSF.

However, at the time of the invention, Stienna et al contemplated a DNA vaccine composition comprising a nucleic acid vector encoding a human Her-2/neu polypeptide, wherein the Her-2/neu polypeptide may lack the intracellular domain (col. 24, lines 45-50; col. 31, lines 30-33; col.s 39-40; col.s 65-67, Example 2). Stienna et al also contemplated the DNA vaccine composition to comprise the cytokine GM-CSF. For example, the nucleic acid used as an immunization agent can also contain regions encoding immunomodulating substances such as the GM-CSF cytokine (col. 17, lines 24-33; col. 25, lines 52-56). Similarly, Pilon et al taught a DNA vaccine composition comprising a nucleic acid encoding a human Her-2/neu polypeptide, wherein the composition further comprised a plasmid expressing the GM-CSF cytokine (pg 3201, col. 2, ¶2; pg 3202, col. 1, DNA immunization).

It would have been obvious to one of ordinary skill in the art to use a DNA vaccine composition comprising a nucleic acid encoding a cytokine, e.g. GM-CSF, with a reasonable chance of success because the art has long recognized the effectiveness of vaccination to utilize various cytokines, e.g. GM-CSF, and co-stimulatory molecules as molecular adjuvants to evoke a tumor-specific CTL response. (Stienna et al, col. 4, lines 8-10).

An artisan would be motivated to use a DNA vaccine composition comprising a nucleic acid encoding a cytokine because Pilon et al teach that without co-stimulation signals, a short-lived cytotoxic T lymphocyte (CTL) response may be induced. Co-expression of GM-CSF may recruit and activate antigen-presenting cells to process and present Her-2/neu epitopes for full CTL activation (pg 3205, col. 2, last ¶), and that an effective anti-tumor response was only observed when a cytokine gene was co-administered. An artisan would also be motivated to use a bicistronic DNA vaccine vector encoding an antigen and a cytokine, either as a fusion protein or through expression of a bicistronic message because the co-expression of cytokine genes with an antigen in a plasmid may increase the local microenvironment concentration of the cytokine in the vicinity of cells that express the antigen gene, which could further augment antigen-specific immunity.

Thus, the invention as a whole is *prima facie* obvious.

Applicant's Arguments

Applicant argues that:

a) the arguments with respect to Piechocki et al and Lee et al are incorporated herein, and

b) Stienna et al and Pilon et al fail to teach a DNA vaccine containing comprising a nucleotide sequence encoding a truncated human Her-2/neu protein, wherein the truncated human Her- 2/neu protein consists of transmembrane and extracellular domains of human Her-2/neu protein, or extracellular domain of the human Her-2/neu protein.

Applicant's argument(s) has been fully considered, but is not persuasive.

With respect to a), the Examiner's response as applied to Piechocki et al and Lee et al are incorporated herein.

With respect to b), Stienna et al and Pilon et al are not required to teach a DNA vaccine containing comprising a nucleotide sequence encoding a truncated human Her-2/neu protein, wherein the truncated human Her- 2/neu protein consists of transmembrane and extracellular domains of human Her-2/neu protein, or extracellular domain of the human Her-2/neu protein because said limitations are taught by Piechocki et al. Rather, Stienna et al and Pilon et al are cited for teaching the combined use of a first nucleic acid encoding a human Her-2/neu polypeptide, e.g. one that may lack the intracellular domain, and a second nucleic acid encoding a cytokine, specifically GM-CSF. Applicant does not contest the teachings in the prior art for combining nucleic acids encoding human Her-2/neu proteins and the cytokine GM-CSF.

Conclusion

6. No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kevin K. Hill, Ph.D. whose telephone number is 571-272-8036. The examiner can normally be reached on Monday through Friday, between 9:00am-6:00pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph T. Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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